AG

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2002 (03.01.2002)

PCT

(10) International Publication Number
WO 02/00217 A1

(51) International Patent Classification[7]: A61K 31/405, A61P 43/00, 25/00 // C07D 209/34

(21) International Application Number: PCT/DK01/00412

(22) International Filing Date: 14 June 2001 (14.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

PA 2000 01022	29 June 2000 (29.06.2000)	DK
PA 2001 00394	8 March 2001 (08.03.2001)	DK

(71) Applicant *(for all designated States except US)*: **NEUROSEARCH A/S** [DK/DK]; 93 Pederstrupvej, DK-2750 Ballerup (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **JENSEN, Bo, Skaaning** [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). **SCHRØDER, Rikke, L.** [DK/DK]; Julius Valentiners vej 13, st. th, DK-2000 Frederiksberg (DK). **STRØBÆK, Dorte** [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). **OLESEN, Søren, Peter** [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK).

(74) Common Representative: **NEUROSEARCH A/S**; Patent Department, 93 Pederstrupvej, DK-2750 Ballerup (DK).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/00217 A1

(54) Title: USE OF 3-SUBSTITUTED OXINDOLE DERIVATIVES AS KCNQ POTASSIUM CHANNEL MODULATORS

(57) Abstract: The present invention relates to the use of substituted 3-phenyl oxindole derivatives having general formula (I), as modulators of the potassium KCNQ channels, to pharmaceutical compositions comprising these compounds, and to methods of treatment herewith.

BNSDOCID: <WO___0200217A1_I_>

USE OF 3-SUBSTITUTED OXINDOLE DERIVATIVES AS KCNQ POTASSIUM CHANNEL MODULATORS

TECHNICAL FIELD

The present invention relates to the use of substituted 3-phenyl oxindole derivatives as modulators of the potassium KCNQ channels, to pharmaceutical compositions comprising these compounds, and to methods of treatment herewith.

BACKGROUND ART

Potassium (K^+) channels are structurally and functionally diverse families of K^+-selective channel proteins, which are ubiquitous in cells, indicating their central importance in regulating a number of key cell functions. While widely distributed as a class, K^+ channels are differentially distributed as individual members of this class or as families.

In general, activation of K^+ channels in cells leads to hyperpolarization of the cell membrane, or in the case of depolarised cells to repolarization, thereby acting as an endogenous membrane voltage clamp. This is of particular importance in excitable cells such as neurons and muscle cells. K^+ channels can respond to important cellular events such as changes in the intracellular concentration of ATP or the intracellular concentration of calcium (Ca^{2+}). The central role of K^+ channels in regulating numerous cell functions makes them particularly important targets for therapeutic development.

Thus EP 477819 describes benzimidazole derivatives useful as openers of the BK_{Ca} channel, and EP 747354 discloses 3-substituted oxindole derivatives useful as maxi-K (BK_{Ca}) channel modulators.

Recently another family of potassium channels, the KCNQ channels, has attracted attention as target for therapeutic development. Thus the human KCNQ1 channel has been disclosed by *Wang, Q et al.* [*Wang, Q et al.*; Nature Genet. 1996 **12** 17-23], the human KCNQ2 channel has been disclosed by *Biervert et al.* [*Biervert et al.*; Science 1998 **279** 403-406]; the human KCNQ3 channel has been disclosed by *Schroeder et al.* [*Schroeder et al.*; Nature 1998 **396** 687-690]; the human KCNQ4 channel has been disclosed by *Kubisch et al.* [*Kubisch et al.*; Cell 1999 **96** (3) 437-46]; and the human KCNQ5 channel has been disclosed by *Schroeder et al.* [*Schroeder et al.*; J. Biol. Chem. on-line 2000 May 17.

Mutated and non-mutated KCNQ2 and KCNQ3 potassium channels have been disclosed in WO 99/07832, WO 99/21875 and WO 99/31232.

BNSDOCID: <WO___0200217A1_I_>

Whereas the BK channels belongs to the Slo subfamily of potassium channels, the KCNQ channels constitute a subfamily belonging to the novel KQT family of potassium channels. The different nature of these channels also is established by the fact that compounds acting on BK channels may not necessarily act on the KCNQ channels, and *vice versa*. Thus BK active compounds like the scorpion toxins show no effect on KCNQ channels, and XE-991 and Linopiridine, while being potent KCNQ inhibiting compounds, show no effect on BK channels.

SUMMARY OF THE INVENTION

According to the present invention it has now been found that a certain group of compounds, formerly known as openers of the BK channels, show excellent KCNQ modulating activities.

It was found, moreover, that these compounds are particular useful for the treatment or alleviation of pain, in particular neuropathic pain, which effect is considered associated with their activity on the KCNQ channels.

In its first aspect the invention relates to the use of a chemical substance capable of affecting a KCNQ channel for the treatment or alleviation of pain, in particular neuropathic pain, chronic headache, central pain, pain related to diabetic neuropathy, to postherpetic neuralgia, or to peripheral nerve injury.

In another aspect the present invention relates to the use of a particular group of 3-substituted oxindole derivatives as modulators of the KCNQ potassium channels, and in particular for the treatment, prevention or alleviation of pain.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

KCNQ activating compounds

In its first aspect, the invention relates to the use of a chemical substance capable of activating a KCNQ channel for the treatment or alleviation of pain, in particular neuropathic pain, chronic headache, central pain, pain related to diabetic neuropathy, to post therapeutic neuralgia, or to peripheral nerve injury.

In the context of this invention a KCNQ activating compound is a substance that is capable of increasing the activity of a KCNQ channel, i.e. the current through the channel, in presence of micromolar or preferably sub-micromolar concentrations of said substance when compared to the activity in absence of said substance, and when determined at physiological conditions.

An increased activity may in particular be determined as an increase of the current obtained under physiologic conditions at any given membrane potential where the channel conducts current under physiological conditions, or as a decreased threshold value for activation of the KCNQ channel.

The activity may be determined by conventional methods for monitoring changes in the membrane potential of a KCNQ channel containing cell, e.g. by electrophysiological methods or by methods based on recording of fluorescence changes.

The KCNQ channel may be a homomeric or heteromeric channel, formed by association of various KCNQ channel subunits, in particular the KCNQ1 subunit, the KCNQ2 subunit, the KCNQ3 subunit, the KCNQ4 subunit and the KCNQ5 subunit.

Preferred homomeric KCNQ channels for use according to the invention are those consisting of KCNQ1 subunits, of KCNQ2 subunits, of KCNQ3 subunits, of KCNQ4 subunits or of KCNQ5 subunits, whereas preferred heteromeric KCNQ channels for use according to the invention are those consisting of KCNQ5 and KCNQ1 channel subunits, of KCNQ5 and KCNQ2 channel subunits, of KCNQ5 and KCNQ3 channel subunits, of KCNQ5 and KCNQ4 channel subunits, of KCNQ5 and KCNQ1 and KCNQ2 channel subunits, of KCNQ5 and KCNQ1 and KCNQ3 channel subunits, of KCNQ5 and KCNQ1 and KCNQ4 channel subunits, of KCNQ5 and KCNQ2 and KCNQ3 channel subunits, of KCNQ5 and KCNQ2 and KCNQ4 channel subunits, of KCNQ5 and KCNQ3 and KCNQ4 channel subunits, of KCNQ5 and KCNQ1 and KCNQ2 and KCNQ3 channel subunits, of KCNQ5 and KCNQ1 and KCNQ2 and KCNQ4 channel subunits, of KCNQ5 and KCNQ1 and KCNQ3 and KCNQ4 channel subunits, or of KCNQ5 and KCNQ2 and KCNQ3 and KCNQ4 channel subunits.

In a preferred embodiment monitoring of the membrane potential of the KCNQ containing cell is performed by patch clamp techniques, e.g. as described by *Hamill, O.P., et al.*, Pflügers Arch. 1981 **351** 85-100.

In other preferred embodiments monitoring of the membrane potential of the KCNQ containing cell is performed using the electrophysiological methods described e.g. in WO 99/19729, in WO 99/31503, in WO 99/34202, in WO 99/64559, in WO 99/66329, in WO 00/34776, in WO 00/71742, or in WO 00/73431.

In another preferred embodiment monitoring of the membrane potential of the KCNQ containing cell is performed using fluorescence methods.

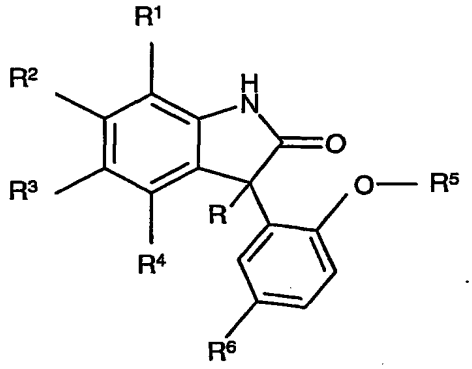
In a preferred embodiment, the KCNQ channel of the KCNQ containing cell is an ion channel that is exogenous to the cell in question, and which cell may in particular be a human embryonic kidney (HEK) cell, a HEK 293 cell, a Chinese

hamster ovary (CHO) cell, a *Xenopus laevis* oocyte (XLO) cell, or any other cell line capable of expressing KCNQ channels.

Oxindole Derivatives

In another aspect the invention relates to oxindole derivatives and their use the use of these compounds for the treatment or alleviation of pain, in particular neuropathic pain, chronic headache, central pain, pain related to diabetic neuropathy, to postherpetic neuralgia, or to peripheral nerve injury.

The 3-substituted oxindole derivatives for use according to the invention may be characterised by the general Formula I



(I)

wherein,

R represents hydrogen, halogen or hydroxy,

R^1, R^2, R^3 and R^4 independently of each another represent hydrogen, halogen alkyl, trihalogenmethyl, phenyl, *p*-methyl-phenyl or *p*-trihalogenmethyl-phenyl, or

R^1 and R^2, R^2 and R^3, or R^3 and R^4 are joined together to form a benzo fused ring,

R^5 represents hydrogen or alkyl, and

R^6 represents halogen or trihalogenmethyl,

or a pharmaceutically-acceptable addition salt thereof.

In a preferred embodiment, the R is hydrogen, fluorine, or a hydroxy group.

In another preferred embodiment, R^1, R^2, R^3 and R^4 independently of each another represent hydrogen, halogen, alkyl, trihalogenmethyl.

In a third preferred embodiment, R^1, R^3 and R^4 represent hydrogen, and R^2 represents halogen, trihalogenmethyl or phenyl.

In a fourth preferred embodiment, R^1 and R^2, R^2 and R^3, or R^3 and R^4 are joined together to form a benzo fused ring.

In a fifth preferred embodiment R^5 is hydrogen or methyl.

In a fourth preferred embodiment R^6 is chlorine.

BNSDOCID: <WO___0200217A1_I_>

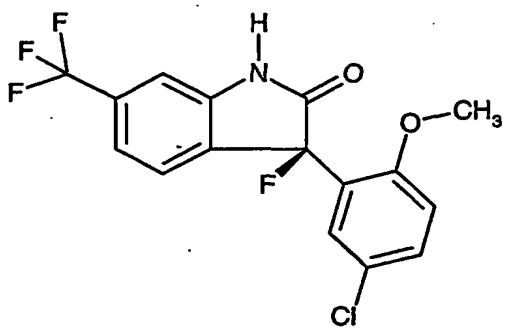
In its most preferred embodiment, the 3-substituted oxindole derivative for use according to the invention is

(+)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-6-(trifluoromethyl)-2H-indol-2-one;
(-)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-6-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-6-(4-methylphenyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-2H-indol-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-4,6-dichloro-1,3-dihydro-2H-indol-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-6-phenyl-2H-indol-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-6-iodo-2H-indol-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-6-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-6-[4-(trifluoromethyl)-phenyl]-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-2H-benz[*e*]indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-2H-benz[*f*]indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-2H-benz[*g*]indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-6-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-4-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-6-(trifluoromethyl)-2H-indol-2-one;
(-)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-6-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-7-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-5-bromo-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-6-iodo-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-4,6-dichloro-1,3-dihydro-3-hydroxy-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-2H-benz[*f*]indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-4,6-*bis*-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-4-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-6-(trifluoromethyl)-2H-indol-2-one;
(+)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-6-(trifluoromethyl)-2H-indol-2-one;

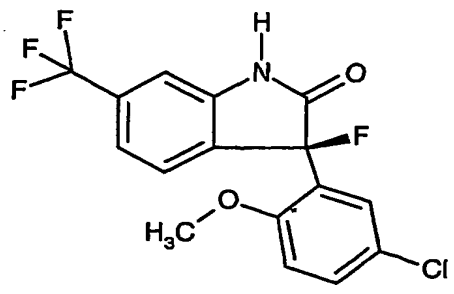
BNSDOCID: <WO___0200217A1_I_>

(-)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-6-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-7-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-4,6-dichloro-1,3-dihydro-3-hydroxy-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-5-bromo-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-6-iodo-2H-indol-2-one;
(±)-1,3-dihydro-3-hydroxy-3-[2-hydroxy-5-(trifluoromethyl)-phenyl]-6-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-2H-benz[*g*]indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-2H-benz[*f*]indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-7-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-phenyl-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-iodo-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-5-methyl-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-5-bromo-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-4,6-*bis*-(trifluoromethyl)-2H-indol-2-one; or
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-fluoro-7-(trifluoromethyl)-2H-indol-2-one.

In its most preferred embodiment, the 3-substituted oxindole derivative for use according to the invention is
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one (Compound 1); or
(3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one (Compound 1A); or
(3R)-(-)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one (Compound 1B),
having the following structures:



or



Definition of Substituents

In the context of this invention halogen represents a fluorine, a chlorine, a bromine or an iodine atom. Thus, a trihalogenmethyl group represents e.g. a trifluoromethyl group and a trichloromethyl group.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to eighteen carbon atoms (C_{1-18}-alkyl), more preferred of from one to six carbon atoms (C_{1-6}-alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C_{1-4}-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a C_{1-3}-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzensulphonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

Metal salts of a chemical compound of the invention includes alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

In the context of this invention the "onium salts" of N-containing compounds are also contemplated as pharmaceutically acceptable salts. Preferred "onium salts" include the alkyl-onium salts, the cycloalkyl-onium salts, and the cycloalkylalkyl-onium salts.

The chemical compound of the invention may be provided in dissoluble or indissoluble forms together with a pharmaceutically acceptable solvents such as water, ethanol, and the like. Dissoluble forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, the dissoluble forms are considered equivalent to indissoluble forms for the purposes of this invention.

Methods of Preparation

The 3-substituted oxindole derivative of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in EP 747354. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Pharmaceutical Compositions

Viewed from one aspect the invention relates to the use of the 3-substituted oxindole derivative of the general Formula I, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of KCNQ channels.

Viewed from another aspect, the invention provides pharmaceutical compositions comprising a therapeutically-effective amount of a 3-substituted oxindole derivative of the general Formula I, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent, for

the treatment, prevention or alleviation of a disease or a disorder or a condition that is responsive to modulation of KCNQ channels.

In a preferred embodiment, the disease, disorder or condition is a disease or adverse condition of the CNS.

In a more preferred embodiment, the disease, disorder or condition include affective disorders, Alzheimer's disease, anxiety, ataxia, CNS damage caused by trauma, stroke or neurodegenerative illness or diseases, cognitive deficits, compulsive behaviour, dementia, HIV dementia, depression, Huntington's disease, mania, cognitive disorders, memory impairment, memory disorders, memory dysfunction, motion disorders, motor disorders, neurodegenerative diseases, Parkinson's disease and Parkinson-like motor disorders, phobias, Pick's disease, psychosis, a bipolar disorder, schizophrenia, spinal cord damage, stroke, torsades de pointes, tremor, muscle spasms, seizures, convulsions, epilepsy, pain, neuropathic pain, central pain, pain related to diabetic neuropathy, to postherpetic neuralgia, or to peripheral nerve injury or drug addiction.

In another preferred embodiment, the disease, disorder or condition is one associated with the heart or skeletal muscle, like heart failure, cardiomyopathia, cardiac arrhythmia, cardiac ischaemia, long QT syndrome, a motion disorder, or a motor disorder, muscle spasms, urinary incontinence, myasthenia gravis, asthma, migraine, tension headache, a bowel disorder, an inflammatory disease, ulcerative colitis, Crohn's disease, Creutzfeld-Jacobs disease, an ophthalmic condition, progressive hearing loss or tinnitus, fever, multiple sclerosis, diabetes, metastatic tumor growth, an obstructive or inflammatory airway disease such as an airway hyperreactivity, a pneumoconiosis such as aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis, a chronic obstructive pulmonary disease (COPD), excerbation of airways hyperreactivity, or cystic firbosis.

In yet another preferred embodiment, the 3-substituted oxindole derivative is used for the treatment, prevention or alleviation of migraine, tension headache, progressive hearing loss, tinnitus, epileptic seizures, or cardiac arrhythmias.

While the 3-substituted oxindole derivative for use according to the invention may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the 3-substituted oxindole derivative, together with one or more pharmaceutically acceptable carriers therefor, and, optionally, other therapeutic

NSDOCID: <WO___0200217A1_I_>

and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route which suite the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition may be prepared by the skilled person using standard and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

Methods of Therapy

In another aspect the invention provides a method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to modulation of KCNQ channels, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of a 3-substituted oxindole derivative of the general Formula I as described above.

In a more preferred embodiment, the disease, disorder or condition include affective disorders, Alzheimer's disease, anxiety, ataxia, CNS damage caused by trauma, stroke or neurodegenerative illness or diseases, cognitive deficits, compulsive behaviour, dementia, HIV dementia, depression, Huntington's disease, mania,

cognitive disorders, memory impairment, memory disorders, memory dysfunction, motion disorders, motor disorders, neurodegenerative diseases, Parkinson's disease and Parkinson-like motor disorders, phobias, Pick's disease, psychosis, a bipolar disorder, schizophrenia, spinal cord damage, stroke, torsades de pointes, tremor, muscle spasms, seizures, convulsions, epilepsy, pain, neuropathic pain, central pain, pain related to diabetic neuropathy, to postherpetic neuralgia, or to peripheral nerve injury or drug addiction.

In another preferred embodiment, the disease, disorder or condition is one associated with the heart or skeletal muscle, like heart failure, cardiomyopathia, cardiac arrhythmia, cardiac ischaemia, long QT syndrome, a motion disorder, or a motor disorder, muscle spasms, urinary incontinence, myasthenia gravis, asthma, migraine, tension headache, a bowel disorder, an inflammatory disease, ulcerative colitis, Crohn's disease, Creutzfeld-Jacobs disease, an ophthalmic condition, progressive hearing loss or tinnitus, fever, multiple sclerosis, diabetes, or metastatic tumor growth, an obstructive or inflammatory airway disease such as an airway hyperreactivity, a pneumoconiosis such as aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis, a chronic obstructive pulmonary disease (COPD), excerbation of airways hyperreactivity, or cystic firbosis.

In yet another preferred embodiment, the 3-substituted oxindole derivative is used for the treatment, prevention or alleviation of migraine, tension headache, progressive hearing loss, tinnitus, epileptic seizures, or cardiac arrhythmias.

It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.005 mg/kg i.v. and 0.01 mg/kg p.o. The upper limit of the dosage range is about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.001 to about 1 mg/kg i.v. and from about 0.1 to about 10 mg/kg p.o.

Biological Activity

According to the present invention, the 3-substituted oxindole derivatives of Formula I above have been found useful as modulators of the KCNQ potassium channels.

At present five such channels are known, i.e. the KCNQ1 channel, the KCNQ2 channel, the KCNQ3 channel, the KCNQ4 channel, and the KCNQ5 channel,

!NSDOCID: <WO___0200217A1_I_>

and heteromeric combinations hereof. Moreover, the modulatory activity may be inhibitory (i.e. inhibitory activity) or stimulating (i.e. activating activity).

In a preferred embodiment the 3-substituted oxindole derivatives of the invention show stimulating activity at the KCNQ2, KCNQ3, KCNQ4 and/or the KCNQ5 potassium channels, and the heteromeric combinations hereof.

The modulatory activity may be determined using conventional methods, e.g. binding or activity studies, known in the art, or as described in the working examples.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention is further illustrated by reference to the accompanying drawing, in which:

Fig. 1 shows the dose-dependent activation of KCNQ4 stably expressed in HEK-293 cells by Compound 1 (0.1, 0.3, 1, 3 and 10 µM, respectively) [Currents; I/nA vs. time/seconds];

Fig. 2 shows the changes in IV relation and activation curve induced by 3 µM Compound 1;

Fig. 3 shows the hyper-polarisation of a KCNQ4 expressing cell by Compound 1; and

Fig. 4 shows the activation of KCNQ5 stably expressed in HEK-293 cells by Compound 1 [Currents; I/nA vs. time/seconds].

EXAMPLES

The invention is further illustrated with reference to the following examples which are not intended to be in any way limiting to the scope of the invention as claimed.

Example 1

Stable Expression of KCNQ4 Channels and KCNQ5 Channels in HEK-293 Cells

KCNQ4 and KCNQ5 was sub-cloned into the mammalian expression vector pNS1n (NeuroSearch), a custom-designed derivative of pcDNA3Neo (InVitrogen). HEK-293 cells (American Type Culture Collection) were grown in DMEM (Life Technologies) supplemented with 10% FCS (Life Technologies) at 37°C in 5% CO_2.

One day prior to transfection, 10^6 cells were plated in a cell culture T25 flask (Nunc). Cells were transfected with 2.5 µg of the plasmid pNS1n_KCNQ4 or with 2.5 µg of the plasmid pNS1n_KCNQ5 using Lipofectamine (Life Technologies)

according to the manufacturer's instructions. Cells transfected with pNS1n_KCNQ4 or pNS1n_KCNQ5 were selected in media supplemented with 0.5 mg/ml geneticin (G418; Life Technologies).

Single clones were picked and propagated in selection media for five passages after which they were considered stable. Following the cells were cultured in regular medium without selection agent.

Expression of functional KCNQ4 channels or KCNQ5 channels was verified by patch-clamp measurements.

Example 2

Electrophysiology

This example demonstrates the electrophysiological activity of a KCNQ4 or a KCNQ5 containing cell, obtained as described in Example 1, when subjected to a compound representative of the invention, (±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one (Compound 1), obtained according to Example 14 of EP 747,354.

Transfected cells were cultured on glass cover slips (Ø=3mm), which were transferred to a small recording chamber. The chamber was perfused with extracellular solutions at a rate of 1 ml/min giving rise to full exchange of the chamber volume (15 µl) each second.

Whole-cell currents were recorded using using a HEKA EPC-9 amplifier and borosilicate glass micropipettes with tip resistances of 1.5-3 MΩ. Series resistances were below 5 MΩ, mostly stayed constant during the experiment and were compensated by 70%. The currents were not leak-subtracted.

All experiments were performed at room temperature (21-25°C). Igor software (WaveMetrics, Lake Oswego, OR) was used for the analysis.

Compound 1 was present in the bath solution during for a period as indicated by the bars, and in the concentrations (µM) listed in Figs. 1-4.

The bath solution consisted of 144 mM NaCl, 4 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$ and 10 mM HEPES (pH adjusted to 7.4). The pipette solution consisted of 144 mM KCl, 5.4 mM $CaCl_2$, 1.8 mM $MgCl_2$, 4 mM NaATP, 0.4 mM GTP, 10 mM EGTA and 10 mM HEPES (pH adjusted to 7.2).

Dose-dependent activation of KCNQ4 (cf. Fig. 1)

The currents were measured in voltage mode using the whole-cell configuration of the patch clamp technique. The holding potential was -90 mV and the currents were elicited by a 1 second depolarising step to -40 mV followed by a 500 msecond step to -60 mV repeated every 5 seconds (upper panel). The panel in the

BNSDOCID: <WO___0200217A1_I_>

middle shows current traces recorded in the absence (control) and in the presence of the indicated concentrations of Compound 1. The lower panel shows the time course of the experiment with the currents recorded at the end of the step to -40 mV (indicated by the arrow in the middle panel) as a function of time.

The result of this experiment is presented in Fig. 1.

Changes in IV Relation and Activation Curve (Fig. 2)

The experimental conditions was as described above, but in this experiment the depolarising potential ranged from -120 mV to +40 mV before a step back to -120 mV where brief inward tail currents were recorded.

The current traces in the absence (control) and in the presence of 3 μM Compound 1 are shown for the steps to -120, -90, -60, -30, 0, and +30 mV. The upper right panel shows the size of the currents measured at the plateau as a function of the depolarising potential.

The IV-relation in the absence of compound is shown as open circles, whereas the IV curve in the presence of 3 μM Compound 1 is shown as closed circles. The lower right panel shows the peak size of the tail currents as a function of the preceding activating potential (Open circles: Control, Closed circles: 3 μM Compound 1).

The result of this experiment is presented in Fig. 2.

Hyperpolarisation of a KCNQ4 Expressing Cell (Fig. 3)

The membrane potential was measured in current clamp mode using the whole cell configuration of the patch clamp technique. A resting membrane potential of around -60 mV was initially recorded from this cell and the addition of 10 μM Compound 1 to the bath solution induced a hyper-polarisation of the membrane potential to -83 mV.

After washout of Compound 1, the membrane potential returned to -69 mV, and subsequent addition of 10 μM Retigabine, a KCNQ activator, induced a faster but smaller hyperpolarisation to a membrane potential of -76 mV.

After washout of Retigabine, 10 μM of XE-991, a potent KCNQ inhibiting compound, was added and this induced a depolarisation to -12 mV, which membrane potential returned very slowly towards the control level upon washout.

The compounds were present in the bath solution during the times indicated by the bars.

The result of this experiment is presented in Fig. 3.

Activation of KCNQ5 in HEK-293 Cells (Fig. 4)

The currents were measured from a cell patch clamped in the whole-cell voltage clamp configuration. The holding potential was -90 mV and the currents were activated by a 2 second depolarising step to -30 mV followed by a 500 msecond step to -60 mV (upper panel).

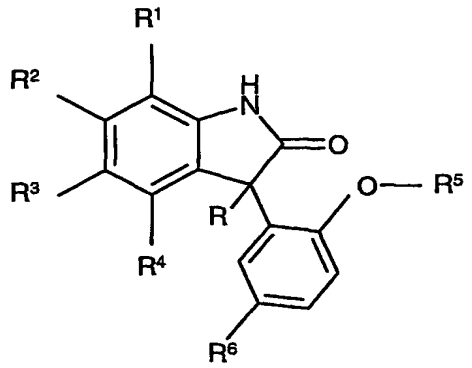
The currents recorded in the absence (control) and in the presence of 10 µM of the reference M current blocker XE-991 is shown in the panel to the left. The panel to the right shows the activation by 10 µM Compound 1 to the same cell after washout of XE-991. The inhibition by XE-991 was not fully reversible and the control current measured immediately before addition of Compound 1 was therefore smaller than the initial control current.

The result of this experiment is presented in Fig. 4.

CLAIMS:

1. Use of a chemical substance capable of activating a KCNQ channel for the treatment or alleviation of pain, in particular neuropathic pain, chronic headache, central pain, chronic headache, pain related to diabetic neuropathy, to postherpetic neuralgia, or to peripheral nerve injury.

2. A pharmaceutical composition comprising a therapeutically-effective amount of a 3-substituted oxindole derivative having the general Formula I,



(I)

wherein,

R represents hydrogen, halogen or hydroxy,

R^1, R^2, R^3 and R^4 independently of each another represent hydrogen, halogen, alkyl, trihalogenmethyl, phenyl, *p*-methyl-phenyl or *p*-trihalogenmethyl-phenyl, or

R^1 and R^2, R^2 and R^3, or R^3 and R^4 are joined together to form a benzo fused ring,

R^5 represents hydrogen or alkyl, and

R^6 represents halogen or trihalogenmethyl,

or a pharmaceutically-acceptable addition salt thereof,

together with at least one pharmaceutically-acceptable carrier or diluent,

for the treatment, prevention or alleviation of a disease or a disorder or a condition that is responsive to modulation of KCNQ channels.

3. The pharmaceutical composition according to claim 1, wherein

R represents hydrogen, halogen or hydroxy,

R^1, R^2, R^3 and R^4 independently of each another represent hydrogen, halogen, alkyl, trihalogenmethyl, phenyl, *p*-methyl-phenyl or *p*-trihalogenmethyl-phenyl,

and when R^1 and R^4 are hydrogen, then R^2 or R^3 is phenyl, *p*-methyl-phenyl or *p*-trihalogenmethyl-phenyl; or

R^1 and R^2, R^2 and R^3, or R^3 and R^4 are joined together to form a benzo fused ring,

R^5 represents hydrogen or alkyl, and

R^6 represents halogen or trihalogenmethyl.

4. The pharmaceutical composition of claim 1, wherein

R^1, R^3 and R^4 represent hydrogen, and

R^2 represents halogen, trihalogenmethyl or phenyl.

5. The pharmaceutical composition of claim 1, wherein

R^1 and R^2, R^2 and R^3, or R^3 and R^4 are joined together to form a benzo fused ring.

6. The pharmaceutical composition of any of claims 1-4, wherein

R^5 is hydrogen or methyl.

7. The pharmaceutical composition of any of claims 1-5, wherein

R^6 is chlorine.

8. The pharmaceutical composition of claim 1, wherein 3-substituted oxindole derivative for use according to the invention is

(+)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-6-(trifluoromethyl)-2H-indol-2-one;

(-)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-6-(trifluoromethyl)-2H-indol-2-one;

(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-6-(4-methylphenyl)-2H-indol-2-one;

(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-2H-indol-one;

(±)-3-(5-chloro-2-hydroxyphenyl)-4,6-dichloro-1,3-dihydro-2H-indol-one;

(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-6-phenyl-2H-indol-one;

(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-6-iodo-2H-indol-one;

(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-6-(trifluoromethyl)-2H-indol-2-one;

BNSDOCID: <WO___0200217A1_I_>

(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-6-[4-(trifluoromethyl)-phenyl]-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-2H-benz[*e*]indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-2H-benz[*f*]indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-2H-benz[*g*]indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-6-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-4-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-6-(trifluoromethyl)-2H-indol-2-one;
(-)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-6-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-7-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-5-bromo-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-6-iodo-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-4,6-dichloro-1,3-dihydro-3-hydroxy-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-hydroxy-2H-benz[*f*]indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-4,6-*bis*-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-4-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-6-(trifluoromethyl)-2H-indol-2-one;
(+)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-6-(trifluoromethyl)-2H-indol-2-one;
(-)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-6-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-7-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-4,6-dichloro-1,3-dihydro-3-hydroxy-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-5-bromo-2H-indol-2-one;

BNSDOCID: <WO___0200217A1_I_>

(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-6-iodo-2H-indol-2-one;
(±)-1,3-dihydro-3-hydroxy-3-[2-hydroxy-5-(trifluoromethyl)-phenyl]-6-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-2H-benz[*g*]indol-2-one;
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-2H-benz[*f*]indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one;
(3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one;
(3R)-(-)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-7-(trifluoromethyl)-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-phenyl-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-iodo-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-5-methyl-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-5-bromo-2H-indol-2-one;
(±)-3-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-4,6-*bis*-(trifluoromethyl)-2H-indol-2-one; or
(±)-3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-fluoro-7-(trifluoromethyl)-2H-indol-2-one;

or a pharmaceutically-acceptable addition salt thereof.

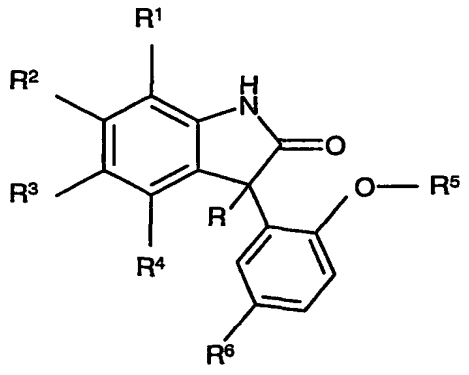
9. The pharmaceutical composition according to any of claims 1-7, wherein the disease, disorder or condition is a disease or adverse condition of the CNS.

10. The pharmaceutical composition according to claim 8, wherein the disease, disorder or condition include affective disorders, Alzheimer's disease, anxiety, ataxia, CNS damage caused by trauma, stroke or neurodegenerative illness or diseases, cognitive deficits, compulsive behaviour, dementia, HIV dementia, depression, Huntington's disease, mania, cognitive disorders, memory impairment, memory disorders, memory dysfunction, motion disorders, motor disorders, neurodegenerative diseases, Parkinson's disease and Parkinson-like motor disorders, phobias, Pick's disease, psychosis, a bipolar disorder, schizophrenia, spinal cord damage, stroke, torsades de pointes, tremor, muscle

spasms, seizures, convulsions, epilepsy, pain, neuropathic pain, central pain, pain related to diabetic neuropathy, to postherpetic neuralgia, or to peripheral nerve injury or drug addiction.

11. The pharmaceutical composition of any of claims 1-7, wherein the disease, disorder or condition is heart failure, cardiomyopathia, cardiac arrhythmia, cardiac ischaemia, long QT syndrome, a motion disorder, or a motor disorder, muscle spasms, urinary incontinence, myasthenia gravis, asthma, migraine, tension headache, a bowel disorder, an inflammatory disease, ulcerative colitis, Crohn's disease, Creutzfeld-Jacobs disease, an ophthalmic condition, progressive hearing loss or tinnitus, fever, multiple sclerosis, diabetes, or metastatic tumor growth, an obstructive or inflammatory airway disease, an airway hyperreactivity, a pneumoconiosis such as aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis, a chronic obstructive pulmonary disease (COPD), excerbation of airways hyperreactivity, or cystic firbosis.

12. A method of treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of KCNQ channels, comprising the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a 3-substituted oxindole derivative having the general Formula I,



(I)

wherein,

R represents hydrogen, halogen or hydroxy,

R^1, R^2, R^3 and R^4 independently of each another represent hydrogen, halogen alkyl, trihalogenmethyl, phenyl, *p*-methyl-phenyl or *p*-trihalogenmethyl-phenyl, or

R^1 and R^2, R^2 and R^3, or R^3 and R^4 are joined together to form a benzo fused ring,
R^5 represents hydrogen or alkyl, and
R^6 represents halogen or trihalogenmethyl,
or a pharmaceutically-acceptable addition salt thereof.

13. The method according to claim 12, wherein the disease, disorder or condition is a disease or adverse condition of the CNS.

14. The method according to claim 13, wherein the disease, disorder or condition include affective disorders, Alzheimer's disease, anxiety, ataxia, CNS damage caused by trauma, stroke or neurodegenerative illness or diseases, cognitive deficits, compulsive behaviour, dementia, HIV dementia, depression, Huntington's disease, mania, cognitive disorders, memory impairment, memory disorders, memory dysfunction, motion disorders, motor disorders, neurodegenerative diseases, Parkinson's disease and Parkinson-like motor disorders, phobias, Pick's disease, psychosis, a bipolar disorder, schizophrenia, spinal cord damage, stroke, torsades de pointes, tremor, muscle spasms, seizures, convulsions, epilepsy, pain, neuropathic pain, central pain, pain related to diabetic neuropathy, to postherpetic neuralgia, or to peripheral nerve injury or drug addiction.

15. The method according to claim 12, wherein the disease, disorder or condition is heart failure, cardiomyopathia, cardiac arrhythmia, cardiac ischaemia, long QT syndrome, a motion disorder, or a motor disorder, muscle spasms, urinary incontinence, myasthenia gravis, asthma, migraine, tension headache, a bowel disorder, an inflammatory disease, ulcerative colitis, Crohn's disease, Creutzfeld-Jacobs disease, an ophthalmic condition, progressive hearing loss or tinnitus, fever, multiple sclerosis, diabetes, or metastatic tumor growth, an obstructive or inflammatory airway disease, an airway hyperreactivity, a pneumoconiosis such as aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis, a chronic obstructive pulmonary disease (COPD), excerbation of airways hyperreactivity, or cystic firbosis.

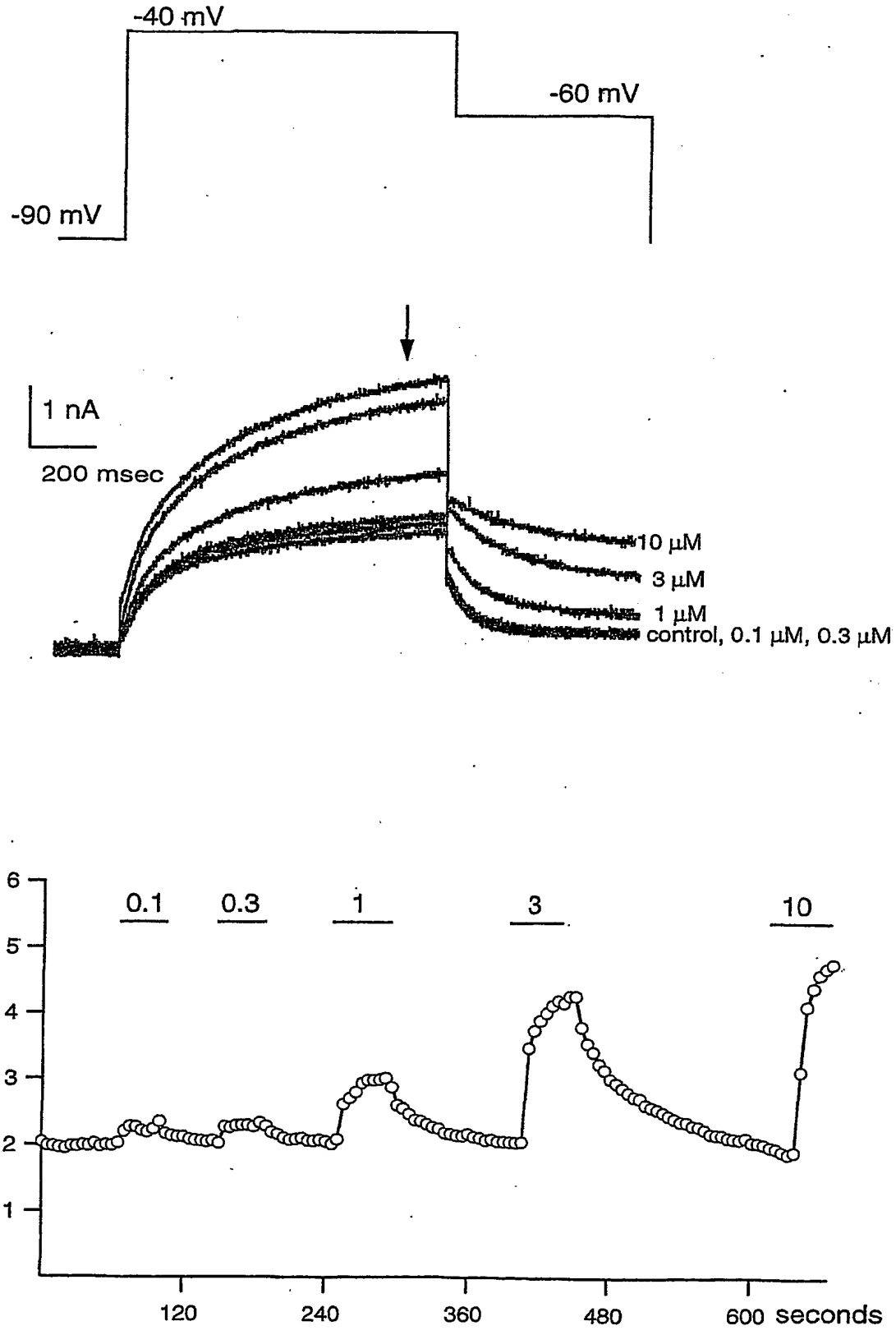


Fig. 1

BNSDOCID: <WO___0200217A1_I_>

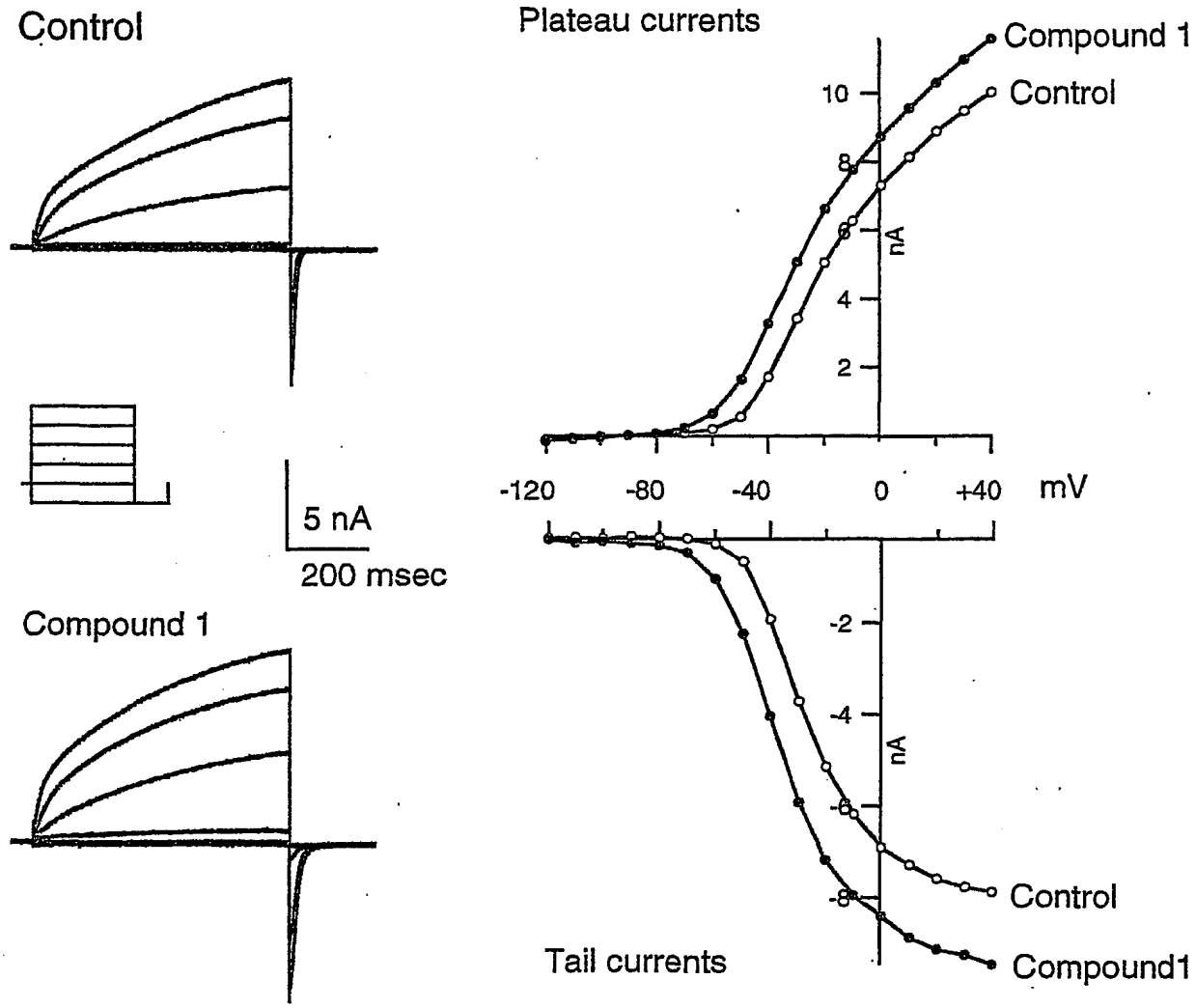


Fig. 2

BNSDOCID: <WO___0200217A1_I_>

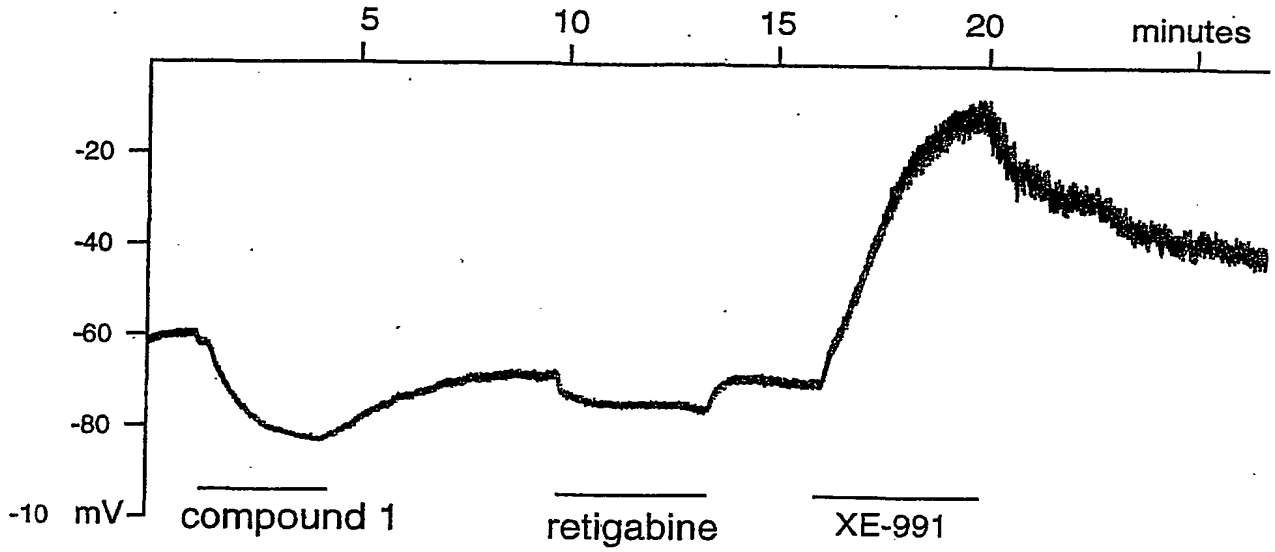


Fig. 3

BNSDOCID: <WO___0200217A1_I_>

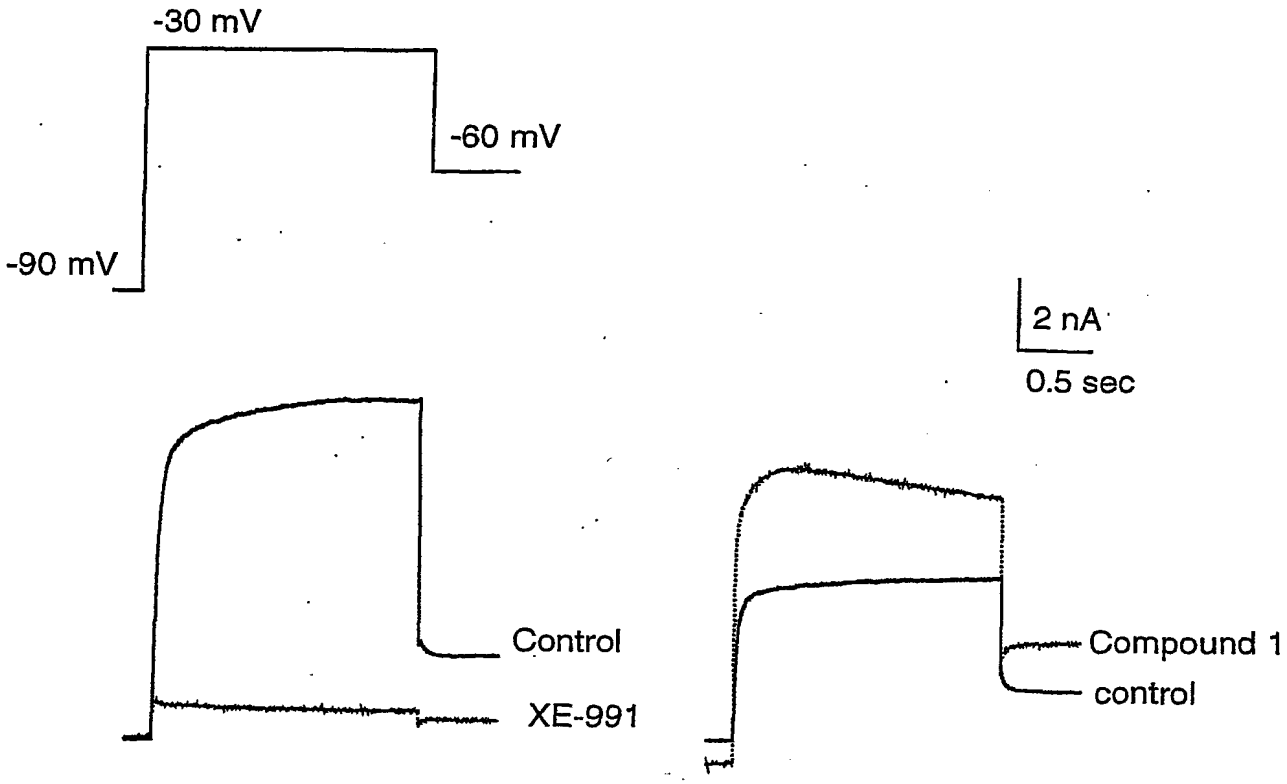


Fig. 4

BNSDOCID: <WO___0200217A1_I_>

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 01/00412

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/405 A61P43/00 A61P25/00 //C07D209/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	RIKKE LOUISE SCHRÖDER ET AL: "KCNQ4 channel activation by BMS-204352 and retigabine" NEUROPHARMACOLOGY, vol. 40, no. 7, June 2001 (2001-06), pages 888-898, XP002901941 the whole document ---	1-15
P,X	VALENTIN K. GRIBKOFF ET AL: "Targeting acute ischemic stroke with a calcium-sensitive opener of maxi-K potassium channels " NATURE MEDICINE, vol. 7, no. 4, April 2001 (2001-04), pages 471-477, XP002901942 the whole document ---	1-15

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 September 2001	07 12 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gerd Strandell

Form PCT/ISA/210 (second sheet) (July 1992)

BNSDOCID: <WO___0200217A1_I_>

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 01/00412

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 10381 A (ICAGEN INC.) 15 February 2001 (2001-02-15) claims 1-9	1
P,X	WO 00 44786 A (NEUROSEARCH AS) 3 August 2000 (2000-08-03) page 1 -page 3 page 16, line 19 -page 17, line 5; claims 40-42	1
X	EP 0 747 354 A (SQUIBB BRISTOL MYERS CO) 11 December 1996 (1996-12-11) the whole document	1-15
X	PIYASENA HEWAWASAM ET AL: "Discovery of a novel class of BK channel openers: Enantiospecific synthesis and BK channel opening activity of 3-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-3-hydroxy-6-(trifluoromethyl)-2H-indol-2-one" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 7, no. 10, 1997, pages 1255-1260, XP002901943 the whole document	1-15
X	WO 98 16222 A (SQUIBB BRISTOL MYERS CO) 23 April 1998 (1998-04-23) page 1, line 10 -page 3, line 12; claims	1-15

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

BNSDOCID: <WO___0200217A1_I_>

INTERNATIONAL SEARCH REPORT

nformation on patent family members

Int tional Application No
PCT/DK 01/00412

Patent docum nt cited in search report	Publication date	Patent family member(s)	Publication date
WO 0110381 A	15-02-2001	AU 6758500 A	05-03-2001
		AU 6758600 A	05-03-2001
		WO 0110380 A2	15-02-2001
		WO 0110381 A2	15-02-2001
WO 0044786 A	03-08-2000	AU 2092700 A	18-08-2000
		WO 0044786 A1	03-08-2000
		EP 1147134 A1	24-10-2001
EP 0747354 A	11-12-1996	US 5565483 A	15-10-1996
		AT 195515 T	15-09-2000
		AU 707760 B2	22-07-1999
		AU 5475796 A	19-12-1996
		BR 1100180 A3	14-03-2000
		CA 2176183 A1	08-12-1996
		CN 1144800 A	12-03-1997
		CZ 9601618 A3	12-03-1997
		DE 69609772 D1	21-09-2000
		DE 69609772 T2	12-04-2001
		DK 747354 T3	18-09-2000
		EP 0747354 A1	11-12-1996
		ES 2148685 T3	16-10-2000
		GR 3034523 T3	29-12-2000
		HU 9601547 A1	29-09-1997
		IL 118349 A	26-07-2000
		JP 8333336 A	17-12-1996
		NO 962232 A	09-12-1996
		NZ 286748 A	26-08-1998
		PL 314672 A1	09-12-1996
		PT 747354 T	30-11-2000
		SG 70572 A1	22-02-2000
		TW 384284 B	11-03-2000
		US 5602169 A	11-02-1997
WO 9816222 A	23-04-1998	AU 728455 B2	11-01-2001
		AU 4734397 A	11-05-1998
		EP 0946173 A1	06-10-1999
		WO 9816222 A1	23-04-1998
		HU 0002449 A2	28-12-2000
		US 5892106 A	06-04-1999
		US 5808095 A	15-09-1998

BNSDOCID: <WO___0200217A1_I_>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 01/00412

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims und r Article 17(2)(a) for the following reas ns:

1. [X] Claims Nos.: 1,12-15
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 1 in partial
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

3NSDOCID: <WO___0200217A1_I_>

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 1,12-15

Claims 1,12-15 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

Continuation of Box I.2

Claims Nos.: 1 in partial

Claims 3-11 are not clear and concise because of the reference to the pharmaceutical composition according to claim 1. Confer PCT, Article 6. However, the search is based on the assumption that the reference is to claim 2.

Present claim 1 relates to the use of any compound defined by reference to a desirable characteristic or property, namely capable of activating a KCNQ channel. Claim 1 covers the use of all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds (compound 1). In the present case, claim 1 so lacks support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, claim 1 also lacks clarity (Article 6 PCT). An attempt is made to define the used compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claim which appear to be clear, supported and disclosed, namely mainly those parts relating to use of the compounds according to claims 2-8.
The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1 (e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is

BNSDOCID: <WO___0200217A1_I_>

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

BNSDOCID: <WO___0200217A1_I_>